



Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from <https://aidsinfo.nih.gov/guidelines> on 8/31/2020

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <https://aidsinfo.nih.gov/e-news>.

Ritonavir (Norvir, RTV)

(Last updated December 24, 2019; last reviewed December 24, 2019)

Animal Studies

Carcinogenicity

Ritonavir (RTV) was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In male mice, a dose-dependent increase in adenomas of the liver and combined adenomas and carcinomas of the liver was observed at RTV doses of 50 mg/kg per day, 100 mg/kg per day, or 200 mg/kg per day; exposure (based on area under the curve) in male mice at the highest dose was approximately 0.3-fold the exposure observed in male humans who received the recommended therapeutic dose. No carcinogenic effects were observed in female mice at exposures that were 0.6-fold the exposures observed in women who received the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 6% of the recommended therapeutic human exposure.¹

Reproduction/Fertility

RTV has had no observed effect on reproductive performance or fertility in rats at drug exposures that were 40% (in males) and 60% (in females) of the exposures achieved with human therapeutic dosing; higher doses were not feasible because of hepatic toxicity in the rodents.¹

Teratogenicity/Adverse Pregnancy Outcomes

No RTV-related teratogenicity has been observed in rats or rabbits. Developmental toxicity, including early resorptions, decreased body weight, ossification delays, and developmental variations (e.g., wavy ribs, enlarged fontanelles) was observed in rats; however, these effects occurred only at maternally toxic dosages (with exposures equivalent to 30% of human therapeutic exposures). In addition, a slight increase in cryptorchidism was noted in rats at exposures equivalent to 22% of human therapeutic exposures. In rabbits, developmental toxicity (i.e., resorptions, decreased litter size, and decreased fetal weight) was also observed only at maternally toxic doses (1.8 times human therapeutic exposure based on body surface area).¹

Placental and Breast Milk Passage

Transplacental passage of RTV has been observed in rats with fetal tissue-to-maternal-serum ratios >1.0 at 24 hours post-dose in mid-gestation and late-gestation fetuses.

Human Studies in Pregnancy

Pharmacokinetics

RTV concentrations were lower during pregnancy than during the postpartum period when RTV was administered to pregnant women with HIV at doses sufficient for HIV suppression (500 mg or 600 mg twice daily) in combination with zidovudine and lamivudine.² RTV concentrations are also reduced during pregnancy compared to postpartum when the drug is used at a low dose (100 mg) to boost the concentrations of other protease inhibitors.^{3,4}

Placental and Breast Milk Passage

In a human placental perfusion model, the clearance index of RTV was very low, with little accumulation in the fetal compartment and no accumulation in placental tissue.⁵ In a Phase 1 study of pregnant women and their infants (PACTG 354), transplacental passage of RTV was minimal, with an average cord blood to maternal plasma concentration ratio of 5.3%.² In a study of cord blood samples from six women who were treated with RTV during pregnancy, the cord blood concentration was less than the assay limit of detection in five of the women and was only 0.38 µg/mL in the remaining woman.⁶ In contrast, in a study of hair and plasma RTV concentrations in 51 mother-infant pairs after lopinavir/ritonavir was administered to the mothers during pregnancy and postpartum, hair and plasma concentrations over time suggested moderate *in utero* transfer of lopinavir but negligible transfer via breastfeeding.⁷

Teratogenicity/Adverse Pregnancy Outcomes

In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to RTV have been

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from <https://aidsinfo.nih.gov/guidelines> on 8/31/2020

monitored to be able to detect at least a 1.5-fold increase in the risk of overall birth defects **and a two-fold increase in the risk of cardiovascular and genitourinary defects (the most common classes of birth defects in the general population)**. No such increase in birth defects has been observed with RTV. Among the cases of first-trimester RTV exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.2% (73 of 3,245 births; 95% confidence interval, 1.8% to 2.8%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.⁸

Excerpt from Table 8

Note: When using FDC tablets, refer to other sections in Appendix B and Table 8 for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations ^a	Use in Pregnancy
Ritonavir (RTV) <i>Norvir</i> (LPV/r) <i>Kaletra</i>	RTV (Norvir) <i>Capsules:</i> • RTV 100 mg <i>Tablets:</i> • RTV 100 mg <i>Oral Solution:</i> • RTV 80 mg/mL <i>Powder:</i> • RTV 100 mg/sachet LPV/r (Kaletra) <i>Tablets:</i> • LPV/r 200 mg/50 mg • LPV/r 100 mg/25 mg <i>Oral Solution:</i> • Each 5 mL contains LPV/r 400 mg/100 mg	Standard Adult Dose of RTV (Norvir) When Used as PK Booster for Other PIs: • RTV 100–400 mg per day in one or two divided doses (refer to other PI sections for specific dosing recommendations) <i>Tablet:</i> • Take with food <i>Capsule or Oral Solution:</i> • To improve tolerability, take with food if possible Standard Adult Doses of LPV/r (Kaletra): • LPV/r 400 mg/100 mg twice daily, or • LPV/r 800 mg/200 mg once daily <i>Tablets:</i> • Take without regard to food. <i>Oral Solution:</i> • Take with food. <i>With EFV or NVP in PI-Naïve or PI-Experienced Patients:</i> • LPV/r 500 mg/125 mg tablets twice daily without regard to meals (use a combination of two LPV/r 200 mg/50 mg tablets and one LPV/r 100 mg/25 mg tablet), or • LPV/r 520 mg/130 mg oral solution (6.5 mL) twice daily with food Pregnancy <i>PKs in Pregnancy:</i> • Lower RTV levels are seen during pregnancy than during postpartum, which may reduce the pharmaco-enhancing effect of RTV in pregnancy. <i>RTV Dosing in Pregnancy:</i> • No dose adjustment necessary when RTV is used as booster. <i>LPV/r Dosing in Pregnancy:</i> • Once-daily dosing is not recommended during pregnancy. • Some experts recommend that an increased dose (i.e., LPV/r 600 mg/150 mg twice daily without regard to meals or LPV/r 500 mg/125 mg twice daily without regard to meals) should be used in the second and third trimesters, especially in PI-experienced pregnant women and women who start treatment during pregnancy with a baseline viral load >50 copies/mL. • When standard dosing is used, monitor virologic response and, if possible, LPV drug levels. For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., LPV/r).	Low placental transfer to fetus. ^b No evidence of increased risk of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). RTV should only be used as low-dose booster for other PIs. RTV oral solution contains 43% alcohol and therefore is not recommended for use during pregnancy, because there is no known safe level of alcohol exposure during pregnancy. LPV/r oral solution contains 42% alcohol and 15% propylene glycol and is not recommended for use in pregnancy. Once-daily LPV/r dosing is not recommended during pregnancy.

^a Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the [Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 10](#)).

^b Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6 **Moderate:** 0.3–0.6 **Low:** <0.3

Key: ARV = antiretroviral; EFV = efavirenz; LPV/r = lopinavir/ritonavir; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RTV = ritonavir

References

1. Ritonavir [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020659s070,022417s022,209512s0051bl.pdf.
2. Scott GB, Rodman JH, Scott WA, et al. Pharmacokinetic and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-10-infected pregnant women and their infants. Presented at: 9th Conference on Retroviruses and Opportunistic Infections. 2002. Seattle, WA.
3. Best BM, Stek AM, Mirochnick M, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr*. 2010;54(4):381-388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20632458>.
4. Mirochnick M, Best BM, Stek AM, et al. Atazanavir pharmacokinetics with and without tenofovir during pregnancy. *J Acquir Immune Defic Syndr*. 2011;56(5):412-419. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21283017>.
5. Casey BM, Bawdon RE. Placental transfer of ritonavir with zidovudine in the ex vivo placental perfusion model. *Am J Obstet Gynecol*. 1998;179(3 Pt 1):758-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9757985>.
6. Mirochnick M, Dorenbaum A, Holland D, et al. Concentrations of protease inhibitors in cord blood after *in utero* exposure. *Pediatr Infect Dis J*. 2002;21(9):835-838. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12352805>.
7. Gandhi M, Mwesigwa J, Aweeka F, et al. Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding. *J Acquir Immune Defic Syndr*. 2013;63(5):578-584. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24135775>.
8. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2019. Wilmington, NC: Registry Coordinating Center. 2019. Available at: <http://www.apregistry.com>.